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 NEWS  6  AUG 18   Data available for download as a PDF in RDISCLOSURE
 NEWS  7  AUG 18   Simultaneous left and right truncation added to PASCAL
 NEWS  8  AUG 18   FROSTI and KOSMET enhanced with Simultaneous Left and Righ
                   Truncation
 NEWS  9  AUG 18   Simultaneous left and right truncation added to ANABSTR
 NEWS 10  SEP 22   DIPPR file reloaded
 NEWS 11  SEP 25   INPADOC: Legal Status data to be reloaded
 NEWS 12  SEP 29   DISSABS now available on STN
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 NEWS 14  OCT 21   BIOSIS file reloaded and enhanced
 NEWS 15  OCT 28   BIOSIS file segment of TOXCENTER reloaded and enhanced

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FILE 'HOME' ENTERED AT 17:11:31 ON 14 NOV 2003

=> file medline, biosis, dgene, wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FILE 'BIOSIS' ENTERED AT 17:11:48 ON 14 NOV 2003
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FILE 'DGENE' ENTERED AT 17:11:48 ON 14 NOV 2003
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=> s annexin
L1        9739 ANNEXIN

=> s MDR or multidrug resistance
L2       27718 MDR OR MULTIDRUG RESISTANCE

=> s l2 and l1
L3          59 L2 AND L1

=> s annexin I
L4         975 ANNEXIN I

=> s l4 and l3
L5           5 L4 AND L3

=> d l5 ti abs ibib tot

L5    ANSWER 1 OF 5  DGENE  COPYRIGHT 2003 THOMSON DERWENT on STN
TI    Modulating or assessing multidrug resistance related
      to annexin proteins
AN    AAY08412  Protein       DGENE
AB    This invention describes a novel human annexin family member,
      P-40 (also known as annexin I) which is a member of
      the MDR (multidrug resistance) gene family,
      for assessing or modulating MDR in a cell. Antisense P-40
      sequences are used to prevent MDR in animals, particularly in
      conjunction with cancer treatment. Detecting levels of the P-40 nucleic
      acid, or related RNA, is used to detect cancer (or pathogens) with
      MDR, or susceptibility. P-40 nucleic acid can also be used as a
      target for identifying therapeutic agents, e.g. antifungal agents, and
      increasing the nucleic acid expression in plants may be used to develop
      specific resistance. The products of the invention have antitumour and
      antifungal activity.
ACCESSION NUMBER: AAY08412  Protein       DGENE
TITLE:            Modulating or assessing multidrug
                  resistance related to annexin proteins
INVENTOR:         Georges E; Wang Y
PATENT ASSIGNEE:  (UYMC-N)UNIV MCGILL.
PATENT INFO:      WO 9921980    A1 19990506                63p
APPLICATION INFO: WO 1998-CA992    19981026
PRIORITY INFO:    CA 1997-2219299  19971024
DOCUMENT TYPE:    Patent
LANGUAGE:         English
OTHER SOURCE:     1999-337419 [28]
CROSS REFERENCES: N-PSDB: AAX57357; AAX57358
DESCRIPTION:      Human p-40/annexin I protein.

L5    ANSWER 2 OF 5  DGENE  COPYRIGHT 2003 THOMSON DERWENT on STN
TI    Modulating or assessing multidrug resistance related
      to annexin proteins
AN    AAX57358  DNA       DGENE
AB    This invention describes a novel human annexin family member,
      P-40 (also known as annexin I) which is a member of
      the MDR (multidrug resistance) gene family,
      for assessing or modulating MDR in a cell. Antisense P-40
```

sequences are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of the P-40 nucleic acid, or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. P-40 nucleic acid can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing the nucleic acid expression in plants may be used to develop specific resistance. The products of the invention have antitumour and antifungal activity.

ACCESSION NUMBER: AAX57358 DNA DGENE
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins
INVENTOR: Georges E; Wang Y
PATENT ASSIGNEE: (UYMC-N)UNIV MCGILL.
PATENT INFO: WO 9921980 A1 19990506 63p
APPLICATION INFO: WO 1998-CA992 19981026
PRIORITY INFO: CA 1997-2219299 19971024
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-337419 [28]
CROSS REFERENCES: P-PSDB: AAY08413
DESCRIPTION: Human p-40/**annexin I** antisense DNA.

L5 ANSWER 3 OF 5 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN
TI Modulating or assessing **multidrug resistance** related to **annexin** proteins
AN AAX57357 DNA DGENE
AB This invention describes a novel human **annexin** family member, P-40 (also known as **annexin I**) which is a member of the **MDR** (**multidrug resistance**) gene family, for assessing or modulating **MDR** in a cell. Antisense P-40 sequences are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of the P-40 nucleic acid, or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. P-40 nucleic acid can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing the nucleic acid expression in plants may be used to develop specific resistance. The products of the invention have antitumour and antifungal activity.

ACCESSION NUMBER: AAX57357 DNA DGENE
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins
INVENTOR: Georges E; Wang Y
PATENT ASSIGNEE: (UYMC-N)UNIV MCGILL.
PATENT INFO: WO 9921980 A1 19990506 63p
APPLICATION INFO: WO 1998-CA992 19981026
PRIORITY INFO: CA 1997-2219299 19971024
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-337419 [28]
CROSS REFERENCES: P-PSDB: AAY08412
DESCRIPTION: Human p-40/**annexin I** DNA.

L5 ANSWER 4 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI Population of cells useful in cell and gene therapy comprise two classes of bone marrow stem cells, small and rapidly self-renewing stem cells, and large more mature marrow stromal cells .
AN 2003-328406 [31] WPIDS
AB US2002168765 A UPAB: 20030516
NOVELTY - A population (I) of small and rapidly self-renewing stem (RS) cells or a population (II) of large, more mature marrow stromal cells (mMSC), is new. The cells within (I) express one or more polypeptides such as vascular endothelial growth factor (VEGF) receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and **annexin** II (lipocortin 2).

DETAILED DESCRIPTION - A population (I) of small and rapidly self-renewing stem (RS) cells or a population (II) of large, more mature marrow stromal cells (mMSC) express one or more polypeptides such as vascular endothelial growth factor (VEGF) receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and **annexin** II (lipocortin 2). The cells within (II) express one or more polypeptides such as STRO-1, platelet-derived growth factor (PDGF) receptor, epidermal growth factor (EGF) receptor, CD10 and CD147.

INDEPENDENT CLAIMS are also included for the following:

(1) Distinguishing a population of small and rapidly self-RS cells from a population of large mMSC, by assessing whether at least 29 polypeptides are expressed in the cells in the RS cell population but are not expressed in the mMSC population, and further at least 9 polypeptides are expressed in the population of MSC, but are not expressed in the population of RS cells, where the RS cells are 7 microns in diameter and the cells within the MSC cell population are 15-50 microns in diameter; and

(2) A population of small and rapidly RS cells and mMSC identified by the above method.

ACTIVITY - None given.

MECHANISM OF ACTION - Cell and gene therapy.

No supporting data is given.

USE - The method is useful for distinguishing a population of small and rapidly self-RS cells from a population of large mMSC (claimed). The two classes of bone marrow stem cells, small rapidly self-renewing stem cells and large more mature marrow stromal cells are useful in cell and gene therapy.

Dwg.0/4

ACCESSION NUMBER: 2003-328406 [31] WPIDS
DOC. NO. CPI: C2003-085353
TITLE: Population of cells useful in cell and gene therapy comprise two classes of bone marrow stem cells, small and rapidly self-renewing stem cells, and large more mature marrow stromal cells .
DERWENT CLASS: B04 D16
INVENTOR(S): COLTER, D C; PROCKOP, D J; SEKIYA, I
PATENT ASSIGNEE(S): (COLT-I) COLTER D C; (PROC-I) PROCKOP D J; (SEKI-I) SEKIYA I
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002168765	A1	20021114	(200331)*		11

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002168765	A1	US 2001-816182	20010323

PRIORITY APPLN. INFO: US 2001-816182 20010323

L5 ANSWER 5 OF 5 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI Modulating or assessing **multidrug resistance** related to **annexin** proteins.
AN 1999-337419 [28] WPIDS
AB WO 9921980 A UPAB: 19990719

NOVELTY - Isolated nucleic acid (I) encoding an **annexin** family member (II), i.e. a member of the **MDR** (**multidrug resistanc**) gene family, for assessing or modulating **MDR** in a cell, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the

following:
(1) a method for detecting and assessing **annexin**-based **MDR** by treating test sample with an oligonucleotide (ON) containing 10-50 nucleotides (nt) that hybridize specifically to RNA and/or DNA encoding an **annexin**, ON being complementary to a sequence of at least 10 consecutive nt from the sequences for annexins I to IX, and detecting any hybrids formed;
(2) kits for this method;
(3) recombinant vector for modulating, inhibiting and/or increasing **annexin**-based **MDR** in a cell, containing (I) linked to a promoter;
(4) cells containing this vector;
(5) a method for identifying compounds that affect **annexin**-based **MDR** by incubating with test compound in presence or absence of a drug and assessing any effect of the test compound on resistance to the drug;
(6) a method of reducing **annexin**-based **MDR** by administering a nucleic acid, (dominant negative) mutant of **annexin**, antibody to **annexin**, peptide or small molecule;
(7) pharmaceutical composition for reducing **MDR** comprising **annexin**-based **MDR**-affecting compound and a carrier; and
(8) methods for diagnosing presence of, or predisposition to, **annexin**-based **MDR** in a patient or pathogen.
ACTIVITY - Antitumor; antifungal.
MECHANISM OF ACTION - None given.
USE - Antisense sequences from (I), or any other agent that inhibits (II), are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of (II), or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. (II) can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing (II) expression in plants may be used to develop specific resistance.
Dwg.0/9

ACCESSION NUMBER: 1999-337419 [28] WPIDS
DOC. NO. NON-CPI: N1999-252873
DOC. NO. CPI: C1999-099183
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): GEORGES, E; WANG, Y
PATENT ASSIGNEE(S): (UYMC-N) UNIV MCGILL; (GEOR-I) GEORGES E; (WANG-I) WANG Y
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9921980	A1	19990506	(199928)*	EN	62
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9896174	A	19990517	(199939)		
CA 2219299	A1	19990424	(199940)	EN	
EP 1025225	A1	20000809	(200039)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9921980	A1	WO 1998-CA992	19981026
AU 9896174	A	AU 1998-96174	19981026

CA 2219299	A1	CA 1997-2219299	19971024
EP 1025225	A1	EP 1998-949842	19981026
		WO 1998-CA992	19981026

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9896174	A	Based on	WO 9921980
EP 1025225	A1	Based on	WO 9921980

PRIORITY APPLN. INFO: CA 1997-2219299 19971024

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FILE 'MEDLINE, BIOSIS, DGENE, WPIDS' ENTERED AT 17:11:48 ON 14 NOV 2003

L1	9739	S	ANNEXIN
L2	27718	S	MDR OR MULTIDRUG RESISTANCE
L3	59	S	L2 AND L1
L4	975	S	ANNEXIN I
L5	5	S	L4 AND L3

=> d l3 ti abs ibib 50-59

L3 ANSWER 50 OF 59 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI 2-Deoxy-D-glucose preferentially kills multidrug-resistant human KB carcinoma cell lines by apoptosis.

AB The aim of this study was to determine the mechanism of cell death associated with the preferential killing of multidrug-resistant (**MDR**) cells by the glycolytic inhibitor 2-deoxy-D-glucose (2DG) in a range of **MDR** human KB carcinoma cell lines selected in different drugs. The D10 values for KB-V1, KB-C1 and KB-A1 (selected in vinblastine, colchicine and doxorubicin respectively) were 1.74, 1.04 and 0.31 mm, respectively, compared with 4.60 mm for the parental cell line (KB-3-1). The mechanism of cell death was identified as apoptosis, based on nuclear morphology, **annexin** V binding and poly(ADP-ribose) polymerase (PARP) cleavage. 2DG induced apoptosis in the three **MDR** cell lines in a dose- and time-dependent manner and did not induce necrosis. PARP cleavage was detected in KB-C1 cells within 2 h of exposure to 50 mm 2DG and slightly later in KB-A1 and KB-V1 cells. The relative levels of 2DG sensitivity did not correlate with the levels of **multidrug resistance** or with the reduced levels of the glucose transporter GLUT-1 in these cells. We speculate that a 2DG-stimulated apoptotic pathway in **MDR** KB cells differs from that in normal KB cells.

ACCESSION NUMBER: 1999:53368 BIOSIS
DOCUMENT NUMBER: PREV199900053368
TITLE: 2-Deoxy-D-glucose preferentially kills multidrug-resistant human KB carcinoma cell lines by apoptosis.
AUTHOR(S): Bell, S. E.; Quinn, D. M.; Kellett, G. L.; Warr, J. R. [Reprint author]
CORPORATE SOURCE: Dep. Biology, University York, P.O. Box 373, York YO10 5YW, UK
SOURCE: British Journal of Cancer, (Dec., 1998) Vol. 78, No. 11, pp. 1464-1470. print.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Feb 1999
Last Updated on STN: 10 Feb 1999

L3 ANSWER 51 OF 59 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

TI Short course infusional idarubicin plus intermittent cytarabine and etoposide for refractory hematologic malignancies: Clinical and preliminary pharmacological results.

AB Background and Objective. Idarubicin (IDA) is relatively immune to the **multidrug resistance** P-gp mechanism that is frequently expressed in recurrent and refractory hematologic malignancies. Owing to rapid metabolism in vivo, a continuous infusion (CI) of IDA might prolong exposure time to the parent drug rather than its more P-gp susceptible alcohol metabolite. For this reason we developed a brief retreatment schedule incorporating CI IDA in order to obtain clinical as well as preliminary pharmacological data in patients with refractory leukemias and lymphomas. Design and Methods. Eligible patients had either advanced-stage acute myeloid or lymphoid leukemias (AML, ALL) or high-grade non-Hodgkin's lymphomas (NHL) which failed curative-intent frontline or salvage regimens in use at our institution during the study period (July-October 1992). CI IDA 5 mg/m2/d was employed together with intermittent (every 8 hours) intermediate-dose cytarabine (500 mg/m2) and etoposide (200 Mg/M2); all drugs were given for 2-4 days. A preliminary pharmacokinetic evaluation of CI IDA was carried out in three patients, including a comparison with bolus delivery in one. The in vitro effects of CI-type vs bolus-type IDA delivery in terms of intracellular IDA accumulation and related pro-apoptotic activity were assessed in P-gp- and P-gp+ human leukemic CEM cells by means of cytofluorimetry (IDA fluorescence Intensity = FI, **annexin** V expression), with and without the addition of P-gp inhibitor cyclosporin A (CsA). Results. Complete (2) or partial (4) responses were achieved in a total of 12 patients (17% and 33%, respectively), despite prior treatments with anthracyclines (100% of cases) and cytarabine-etoposide (33% of cases). Hematological toxicity caused the duration of treatment to be reduced from 4 days to 2 days after the first 4 patients. The procedural death rate was 42% (5/12), which was probably related in part to the sum of adverse prognostic characteristics: median patient age 55 years, two-thirds of cases having previously failed second/third-line regimens. The pharmacokinetic study showed an increased plasma AUC value with CI IDA in one patient (2.9-fold increase vs bolus delivery) due to the prolonged presence of low IDA plasma levels (10-20 ng/mL vs 50 ng/mL), as seen in two other cases as well. On the other hand, the in vitro study did not prove to be in favor of CI IDA because the R threshold (>1500 units) associated with increased apoptosis of P-gp, cells (>10%) was achieved only with bolus-type IDA exposure (50 ng/mL for 30') plus CsA. Interpretation and conclusions. This short regimen demonstrated activity against end-stage leukemias and lymphomas and might prove to be more effective and less toxic In younger patients and in those with less advanced disease. In view of the results from plasma pharmacokinetics and in vitro intracellular IDA accumulation and apoptosis assays in lymphoblastic CEM cells, CI IDA 5 mg/m2/day may not represent a better therapeutic option than a rapid bolus injection, particularly in P-gp+ neoplasms. If obtaining an adequate intracellular drug concentration is the primary treatment goal, a higher CI IDA dosage, the addition of a P-gp down-regulator such as CsA and others, and an in vivo study focusing on tumor samples from patients could all be helpful.

ACCESSION NUMBER: 1998:217080 BIOSIS
DOCUMENT NUMBER: PREV199800217080

TITLE: Short course infusional idarubicin plus intermittent cytarabine and etoposide for refractory hematologic malignancies: Clinical and preliminary pharmacological results.

AUTHOR(S): Bassan, Renato [Reprint author]; Chiodini, Barbara; Zucchetti, Massimo; Lerede, Teresa; Cornelli, Pier Emilio; Cortelazzo, Sergio; Barbui, Tiziano

CORPORATE SOURCE: Div. Ematologia, Ospedali Riuniti, Largo Barozzi 1, 24100 Bergamo, Italy

SOURCE: Haematologica, (Jan., 1998) Vol. 83, No. 1, pp. 27-33.

print.
CODEN: HAEMAX. ISSN: 0390-6078.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 11 May 1998
Last Updated on STN: 11 May 1998

L3 ANSWER 52 OF 59 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
TI THE 1991 MERCK FROSST AWARD **MULTIDRUG RESISTANCE** IN SMALL CELL LUNG CANCER.
AB The two-year survival rate of patients with small cell lung cancer is less than 10%. The major reason for this poor outcome is the development of drug resistance. Panels of small cell lung cancer cell lines have been established, providing models for the study of drug resistance in this tumour. One such model is the doxorubicin-selected H69AR cell line. H69AR displays the typical **multidrug resistance** phenotype in that it is cross-resistant to anthracyclines, Vinca alkaloids (e.g., vinblastine) and epipodophyllotoxins (e.g. VP-16). However, H69AR cells do not overexpress P-glycoprotein, the membrane drug efflux pump frequently found on multidrug resistant cells. Some alterations in glutathione levels and associated enzyme activities were found but the data do not support the notion that enhanced drug detoxication is involved in H69AR cell resistance. Fewer drug-induced DNA strand breaks, reduced levels of topoisomerase II, and reduced formation of drug-stabilized DNA/topoisomerase II complexes were observed in H69AR cells. These data implicate topoismerase II in the resistance phenotype of H69AR cells, but cannot explain H69AR cell resistance to the Vinca alkaloids, which do not have topoisomerase II as a target. Monoclonal antibodies against antigens overexpressed on H69AR cells have been derived and four have been characterized. Immunoscreening of an H69AR cDNA expression library was allowed the identification of one of these antigens as p36 (**annexin** II), a Ca2+/phospholipid binding protein. Chemosensitizers and novel xenobiotics have been examined for their ability to circumvent the drug resistance of H69AR cells. The limited success of these investigations suggests that innovative approaches may be required. In conclusion, the data obtained with H69AR and other models of small cell lung cancer indicate that multiple mechanisms contribute to drug resistance in this disease.
ACCESSION NUMBER: 1992:282892 BIOSIS
DOCUMENT NUMBER: PREV199294007542; BA94:7542
TITLE: THE 1991 MERCK FROSST AWARD **MULTIDRUG RESISTANCE** IN SMALL CELL LUNG CANCER.
AUTHOR(S): COLE S P C [Reprint author]
CORPORATE SOURCE: CANCER RES LAB, QUEEN'S UNIV, KINGSTON, ONT, CANADA K7L 3N6
SOURCE: Canadian Journal of Physiology and Pharmacology, (1992) Vol. 70, No. 3, pp. 313-329.
CODEN: CJPPA3. ISSN: 0008-4212.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 10 Jun 1992
Last Updated on STN: 9 Aug 1992

L3 ANSWER 53 OF 59 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN
TI Modulating or assessing **multidrug resistance** related to **annexin** proteins
AN AAY08412 Protein DGENE
AB This invention describes a novel human **annexin** family member, P-40 (also known as **annexin** I) which is a member of the **MDR** (**multidrug resistance**) gene family, for assessing or modulating **MDR** in a cell. Antisense P-40 sequences are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of the P-40 nucleic acid, or related RNA, is used to detect cancer (or pathogens) with **MDR**,

or susceptibility. P-40 nucleic acid can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing the nucleic acid expression in plants may be used to develop specific resistance. The products of the invention have antitumour and antifungal activity.

ACCESSION NUMBER: AAY08412 Protein DGENE
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins
INVENTOR: Georges E; Wang Y
PATENT ASSIGNEE: (UYMC-N)UNIV MCGILL.
PATENT INFO: WO 9921980 A1 19990506 63p
APPLICATION INFO: WO 1998-CA992 19981026
PRIORITY INFO: CA 1997-2219299 19971024
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-337419 [28]
CROSS REFERENCES: N-PSDB: AAX57357; AAX57358
DESCRIPTION: Human p-40/**annexin** I protein.

L3 ANSWER 54 OF 59 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN
TI Modulating or assessing **multidrug resistance** related to **annexin** proteins
AN AAX57358 DNA DGENE
AB This invention describes a novel human **annexin** family member, P-40 (also known as **annexin** I) which is a member of the **MDR** (**multidrug resistance**) gene family, for assessing or modulating **MDR** in a cell. Antisense P-40 sequences are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of the P-40 nucleic acid, or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. P-40 nucleic acid can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing the nucleic acid expression in plants may be used to develop specific resistance. The products of the invention have antitumour and antifungal activity.

ACCESSION NUMBER: AAX57358 DNA DGENE
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins
INVENTOR: Georges E; Wang Y
PATENT ASSIGNEE: (UYMC-N)UNIV MCGILL.
PATENT INFO: WO 9921980 A1 19990506 63p
APPLICATION INFO: WO 1998-CA992 19981026
PRIORITY INFO: CA 1997-2219299 19971024
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-337419 [28]
CROSS REFERENCES: P-PSDB: AAY08413
DESCRIPTION: Human p-40/**annexin** I antisense DNA.

L3 ANSWER 55 OF 59 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN
TI Modulating or assessing **multidrug resistance** related to **annexin** proteins
AN AAX57357 DNA DGENE
AB This invention describes a novel human **annexin** family member, P-40 (also known as **annexin** I) which is a member of the **MDR** (**multidrug resistance**) gene family, for assessing or modulating **MDR** in a cell. Antisense P-40 sequences are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of the P-40 nucleic acid, or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. P-40 nucleic acid can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing the nucleic acid expression in plants may be used to develop specific resistance. The products of the invention have antitumour and antifungal

activity.
ACCESSION NUMBER: AAX57357 DNA DGENE
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins
INVENTOR: Georges E; Wang Y
PATENT ASSIGNEE: (UYMC-N)UNIV MCGILL.
PATENT INFO: WO 9921980 A1 19990506 63p
APPLICATION INFO: WO 1998-CA992 19981026
PRIORITY INFO: CA 1997-2219299 19971024
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 1999-337419 [28]
CROSS REFERENCES: P-PSDB: AAY08412
DESCRIPTION: Human p-40/**annexin** I DNA.

L3 ANSWER 56 OF 59 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI Population of cells useful in cell and gene therapy comprise two classes of bone marrow stem cells, small and rapidly self-renewing stem cells, and large more mature marrow stromal cells .
AN 2003-328406 [31] WPIDS
AB US2002168765 A UPAB: 20030516
NOVELTY - A population (I) of small and rapidly self-renewing stem (RS) cells or a population (II) of large, more mature marrow stromal cells (mMSC), is new. The cells within (I) express one or more polypeptides such as vascular endothelial growth factor (VEGF) receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and **annexin** II (lipocortin 2).

DETAILED DESCRIPTION - A population (I) of small and rapidly self-renewing stem (RS) cells or a population (II) of large, more mature marrow stromal cells (mMSC) express one or more polypeptides such as vascular endothelial growth factor (VEGF) receptor-2 (FLK-1), TRK (an NGF receptor), transferrin receptor, and **annexin** II (lipocortin 2). The cells within (II) express one or more polypeptides such as STRO-1, platelet-derived growth factor (PDGF) receptor, epidermal growth factor (EGF) receptor, CD10 and CD147.

INDEPENDENT CLAIMS are also included for the following:

(1) Distinguishing a population of small and rapidly self-RS cells from a population of large mMSC, by assessing whether at least 29 polypeptides are expressed in the cells in the RS cell population but are not expressed in the mMSC population, and further at least 9 polypeptides are expressed in the population of MSC, but are not expressed in the population of RS cells, where the RS cells are 7 microns in diameter and the cells within the MSC cell population are 15-50 microns in diameter; and

(2) A population of small and rapidly RS cells and mMSC identified by the above method.

ACTIVITY - None given.

MECHANISM OF ACTION - Cell and gene therapy.

No supporting data is given.

USE - The method is useful for distinguishing a population of small and rapidly self-RS cells from a population of large mMSC (claimed). The two classes of bone marrow stem cells, small rapidly self-renewing stem cells and large more mature marrow stromal cells are useful in cell and gene therapy.

Dwg.0/4
ACCESSION NUMBER: 2003-328406 [31] WPIDS
DOC. NO. CPI: C2003-085353
TITLE: Population of cells useful in cell and gene therapy comprise two classes of bone marrow stem cells, small and rapidly self-renewing stem cells, and large more mature marrow stromal cells .
DERWENT CLASS: B04 D16
INVENTOR(S): COLTER, D C; PROCKOP, D J; SEKIYA, I
PATENT ASSIGNEE(S): (COLT-I) COLTER D C; (PROC-I) PROCKOP D J; (SEKI-I)

SEKIYA I
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002168765	A1	20021114	(200331)*		11

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002168765	A1	US 2001-816182	20010323

PRIORITY APPLN. INFO: US 2001-816182 20010323

L3 ANSWER 57 OF 59 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI New conjugated polymer tag complexes, useful for detecting analytes in a sample, have fluorescent optical labels attached to amino acid monomer units.
AN 2001-367253 [38] WPIDS
AB WO 200127625 A UPAB: 20010711
NOVELTY - Water soluble polymer (A) of known composition and sequence linked to and selectively cleaved from a solid support comprises a cleavage segment next to the support, a second segment able to covalently couple to a tag, and a third segment able to covalently bond to an analyte-binding species or an analyte.

DETAILED DESCRIPTION - Water soluble polymer (A) of known composition and sequence linked to and selectively cleaved from a solid support comprises a cleavage segment next to the support made of at least one monomer unit, a second segment of at least one monomer unit linked to a reactive functionality able to covalently couple to a tag, and a third segment comprising at least one monomer unit linked to a reactive functionality able to covalently bond to an analyte-binding species or an analyte.

INDEPENDENT CLAIMS are also included for:

(1) a tagged water soluble polymer (B) linked to and selectively cleaved from a solid support comprises a cleavage segment next to the support, a second segment able to covalently couple to a tag, and a third segment able to covalently bond to an analyte-binding species or an analyte;

(2) polymer (B) of formula (III) cleaved from the solid support;

(3) preparation of a conjugate of an analyte-binding species and a tagged water soluble polymer comprising: synthesis of a water soluble polymer linked to a solid support; when necessary, specifically reacting at least one monomer unit with one or more tags; specifically reacting at least one monomer unit with an analyte-binding species; and selectively cleaving the polymer from the solid support;

(4) preparation of a tagged water soluble polymer comprising at least two monomer units linked to a reactive functionality and at least one spacer unit and at least one monomer unit linked to an optical label capable of emitting and/or absorbing light, comprising: reacting a monomer containing 2-3 reactive functionalities of which all but one are protected with a solid support; deprotecting; reacting the product with a second monomer containing 2-3 reactive functionalities of which all but one are protected; deprotecting; repeating with further monomer units; cleaving polymer from support; and deprotecting reactive functionalities, where at least one monomer is linked to an optical label capable of absorbing and/or emitting light between 200-1400 nm;

(5) a method for detecting an analyte by linking the analyte to an analyte-binding species linked to polymer (B); and

(6) preparation of (III) by modeling a sequence of amino acids to optimize distance and geometry between fluorescent optical labels,

synthesizing polymers by combinatorial methods, screening polymers by fluorescence and/or luminescence spectra for maximum desired emission to determine potential candidates to be optical labels in tagged peptides, synthesizing (A), cleaving polymer from the support, coupling an analyte binding species, cleaving optically labeled polymer, and utilizing the polymer conjugate.

USE - To detect an analyte in a sample by fluorescence (claimed).

Dwg.0/0

ACCESSION NUMBER: 2001-367253 [38] WPIDS
DOC. NO. NON-CPI: N2001-267990
DOC. NO. CPI: C2001-112561
TITLE: New conjugated polymer tag complexes, useful for detecting analytes in a sample, have fluorescent optical labels attached to amino acid monomer units.
DERWENT CLASS: A23 A96 B04 D16 S03
INVENTOR(S): FRANSON, R C; LEIF, R C; VALLARINO, L M; VALLARINO, L
PATENT ASSIGNEE(S): (FRAN-I) FRANSON R C; (LEIF-I) LEIF R C; (VALL-I) VALLARINO L M; (VALL-I) VALLARINO L
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001027625	A1	20010419	(200138)*	EN	104
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA CH DE FI GB JP US					
EP 1221052	A1	20020710	(200253)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001027625	A1	WO 2000-US27787	20001007
EP 1221052	A1	EP 2000-968871	20001007
		WO 2000-US27787	20001007

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1221052	A1 Based on	WO 2001027625

PRIORITY APPLN. INFO: US 1999-158718P 19991008

L3 ANSWER 58 OF 59 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI New spectrofluorometrically detectable luminescent composition, useful for detecting e.g. vitamins, hormones, pharmaceuticals, drugs, pesticides, proteins or nucleic acids.
AN 2000-505733 [45] WPIDS
AB WO 200042048 A UPAB: 20021014
NOVELTY - A novel spectrofluorimetrically detectable luminescent composition comprises water, a micelle-producing amount of at least one surfactant, at least one energy transfer acceptor lanthanide element macrocycle compound (EALM) having an emission spectrum peak of 500-950 nm, and at least one energy transfer donor compound of yttrium or a 3-valent lanthanide element having atomic number 59-71.

DETAILED DESCRIPTION - A novel spectrofluorimetrically detectable luminescent composition comprises water, a micelle-producing amount of at least one surfactant, at least one energy transfer acceptor lanthanide element macrocycle compound (EALM) (at least 1 x 10-10 moles/liter) having an emission spectrum peak of 500-950 nm, and a luminescence-enhancing amount of at least one energy transfer donor compound of yttrium or a 3-valent lanthanide element having atomic number 59-71, provided that the

lanthanide element of the macrocycle compound and the lanthanide element of the energy transfer donor compound are not identical.

An INDEPENDENT CLAIM is also included for a method for analysis of a sample containing or suspected of containing at least one analyte, frequently a biologically active compound, the method comprising:

(a) contacting the sample with a functionalized complex of a metal M, where M is a metal ion selected from a lanthanide having atomic number 57-71, and actinide having atomic number 89-103, and yttrium (III) having atomic number 39; in a reaction medium under binding conditions, whereby the analyte when present either interacts with the complex to form a conjugate or competes for interaction with a binding material specific for interaction with the complex and with the analyte;

(b) adding to the reaction medium a luminescence-enhancing amount of at least one energy transfer donor compound of yttrium or a 3-valent lanthanide element having atomic number 59-71, provided that the lanthanide element of the macrocycle compound and a lanthanide element of the energy transfer donor compound are not identical;

(c) subjecting the reaction medium to excitation energy in the range of 200-400 nm, whereby enhanced luminescence in the range of 500-950 nm is generated;

(d) monitoring the luminescence of the reaction medium to measure in the sample: (i) the presence and/or concentration of the conjugate; (ii) the presence and/or concentration of the product of the interaction of the complex with the binding material; and/or (iii) the presence and/or concentration of the product of the interaction of the conjugate with the binding material.

USE - The method can be used for the detection of analytes such as vitamins, vitamin precursors, and vitamin metabolites including retinal, vitamin K, cobalamin, biotin folate; hormones and related compounds including steroid hormones including estrogen, corticosterone, testosterone, ecdysone; amino acid derived hormones including thyroxine, epinephrine; prostaglandins; peptide hormones including oxytocin, somatostatin; pharmaceuticals including aspirin, penicillin, hydrochlorothiazide; nucleic acid constituents including natural and synthetic nucleic acid bases including cytosine, thymine, adenine, guanine, uracil, derivatives of the bases including 5-bromouracil, natural and synthetic nucleosides and deoxynucleosides including 2-deoxyadenosine, 2-deoxycytidine, 2-deoxythymidine, 2-deoxyguanosine, 5-bromo-2-deoxyuridine, adenosine, cytidine, uridine, guanosine, 5-bromouridine; drugs of abuse including cocaine, tetrahydrocannabinol; histological stains including fluorescein, DA PI, pesticides including digitoxin; and miscellaneous haptens including diphenylhydantoin, quinidine, RDX; polyaminoacids, polypeptides, proteins, polysaccharides, nucleic acids, glycosaminoglycans, glycoproteins, ribosomes, and proteins and their combinations including albumins, globulins, hemoglobin, staphylococcal protein A, alpha-feto-protein, retinal-binding protein, avidin, streptavidin, C-reactive protein, collagen, keratin; immunoglobulins including IgG, IgM, AgA, IgE; hormones including lymphokines, follicle stimulating hormone, and thyroid stimulating hormone; enzymes including trypsin, peptide, reverse transcriptases; cell surface antigens on T- and B-lymphocytes, i.e. CD-4, CD-8, CD-20 proteins, and the leukocyte cell surface antigens; blood group antigens including A, B and Rh; major histocompatilibity antigens both of class 1 and 2; hormone receptors including estrogen receptor, progesterone receptor, and glucocorticoid receptor; cell cycle associated proteins including protein kinases, cyclins, PCNA, p53; antigens associated with cancer diagnosis and therapy including BRCA(s) carcinoembryonic antigen, HPV 16, HPV 18, **MDR**, c-neu, tumor suppressor proteins, p53 and retinalblastoma; apoptosis related markers including **annexin** V, bak, bcl-2, fas caspases, nuclear matrix protein, cytochrome c, nucleosome; toxins including cholera toxin, diphtheria toxin, botulinum toxin, snake venom toxins, tetrodotoxin, saxitoxin; lectins including concanavalin, wheat germ agglutinin, soy bean agglutinin; polysialic acids including chitin; polynucleotides including RNAs including segments of the HIV genome, human

hemoglobin A, mRNA, DNAs including chromosome specific sequences, centromeres, telomere specific sequences, single copy sequences from normal tissues, or single copy sequences from tumors (claimed). The compositions can also be used in analytical cytology, histological staining and imaging processing.

ADVANTAGE - The compositions do not require the prior dissociation of the luminescence-enhanced complex before measuring its emission spectrum, and do not require time-gated detection systems. Using the method, 2 different analytes can be measured in the presence of one another.

Dwg.0/15

ACCESSION NUMBER: 2000-505733 [45] WPIDS
DOC. NO. CPI: C2000-151733
TITLE: New spectrofluorometrically detectable luminescent composition, useful for detecting e.g. vitamins, hormones, pharmaceuticals, drugs, pesticides, proteins or nucleic acids.
DERWENT CLASS: B02 B04 D16
INVENTOR(S): LEIF, R C; VALLARINO, L M; VALLARINO, L
PATENT ASSIGNEE(S): (LEIF-I) LEIF R C; (VALL-I) VALLARINO L M; (VALL-I) VALLARINO L
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000042048	A1	20000720	(200045)*	EN	94
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA CH DE FI GB JP US					
EP 1150985	A1	20011107	(200168)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 6340744	B1	20020122	(200208)		
US 2002132992	A1	20020919	(200264)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000042048	A1		WO 2000-US1211	20000118
EP 1150985	A1		EP 2000-905653	20000118
			WO 2000-US1211	20000118
US 6340744	B1	Provisional	US 1999-116316P	19990119
			US 2000-484670	20000118
US 2002132992	A1	Provisional	US 1999-116316P	19990119
		Cont of	US 2000-484670	20000118
			US 2001-10597	20011206

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1150985	A1	Based on	WO 2000042048
US 2002132992	A1	Cont of	US 6340744

PRIORITY APPLN. INFO: US 2000-484670 20000118; US 1999-116316P 19990119; US 2001-10597 20011206

L3 ANSWER 59 OF 59 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
TI Modulating or assessing **multidrug resistance** related to **annexin** proteins.
AN 1999-337419 [28] WPIDS
AB WO 9921980 A UPAB: 19990719

NOVELTY - Isolated nucleic acid (I) encoding an **annexin** family member (II), i.e. a member of the **MDR** (**multidrug resistance**) gene family, for assessing or modulating **MDR**

in a cell, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method for detecting and assessing **annexin**-based **MDR** by treating test sample with an oligonucleotide (ON) containing 10-50 nucleotides (nt) that hybridize specifically to RNA and/or DNA encoding an **annexin**, ON being complementary to a sequence of at least 10 consecutive nt from the sequences for annexins I to IX, and detecting any hybrids formed;

(2) kits for this method;

(3) recombinant vector for modulating, inhibiting and/or increasing **annexin**-based **MDR** in a cell, containing (I) linked to a promoter;

(4) cells containing this vector;

(5) a method for identifying compounds that affect **annexin**-based **MDR** by incubating with test compound in presence or absence of a drug and assessing any effect of the test compound on resistance to the drug;

(6) a method of reducing **annexin**-based **MDR** by administering a nucleic acid, (dominant negative) mutant of **annexin**, antibody to **annexin**, peptide or small molecule;

(7) pharmaceutical composition for reducing **MDR** comprising **annexin**-based **MDR**-affecting compound and a carrier; and

(8) methods for diagnosing presence of, or predisposition to, **annexin**-based **MDR** in a patient or pathogen.

ACTIVITY - Antitumor; antifungal.

MECHANISM OF ACTION - None given.

USE - Antisense sequences from (I), or any other agent that inhibits (II), are used to prevent **MDR** in animals, particularly in conjunction with cancer treatment. Detecting levels of (II), or related RNA, is used to detect cancer (or pathogens) with **MDR**, or susceptibility. (II) can also be used as a target for identifying therapeutic agents, e.g. antifungal agents, and increasing (II) expression in plants may be used to develop specific resistance.

Dwg.0/9

ACCESSION NUMBER: 1999-337419 [28] WPIDS
DOC. NO. NON-CPI: N1999-252873
DOC. NO. CPI: C1999-099183
TITLE: Modulating or assessing **multidrug resistance** related to **annexin** proteins.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): GEORGES, E; WANG, Y
PATENT ASSIGNEE(S): (UYMC-N) UNIV MCGILL; (GEOR-I) GEORGES E; (WANG-I) WANG Y
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9921980	A1	19990506	(199928)*	EN	62
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9896174	A	19990517	(199939)		
CA 2219299	A1	19990424	(199940)	EN	
EP 1025225	A1	20000809	(200039)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 9921980	A1	WO 1998-CA992	19981026
AU 9896174	A	AU 1998-96174	19981026
CA 2219299	A1	CA 1997-2219299	19971024
EP 1025225	A1	EP 1998-949842	19981026
		WO 1998-CA992	19981026

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9896174	A	Based on	WO 9921980
EP 1025225	A1	Based on	WO 9921980

PRIORITY APPLN. INFO: CA 1997-2219299 19971024

=> d his

(FILE 'HOME' ENTERED AT 17:11:31 ON 14 NOV 2003)

FILE 'MEDLINE, BIOSIS, DGENE, WPIDS' ENTERED AT 17:11:48 ON 14 NOV 2003
L1 9739 S ANNEXIN
L2 27718 S MDR OR MULTIDRUG RESISTANCE
L3 59 S L2 AND L1
L4 975 S ANNEXIN I
L5 5 S L4 AND L3

=> d l3 ti abs ibib 1-15

L3 ANSWER 1 OF 59 MEDLINE on STN
TI In vitro antileukemic effect of a new anthracycline analogue, MEN 11079.
AB The biological activity of MEN 11079, a new daunorubucin analogue with a fluorine atom in C(8) of ring A, was investigated in the human leukemic cell lines K-562 and in mononuclear cells (MNCs) of 40 patients with acute myeloid leukemia (AML) and the activity compared to two well-characterized anthracyclines, idarubicin (IDA) and doxorubicin (DOXO). IDA and MEN 11079 were more active than DOXO in cytotoxicity tests (WST-1 assay). IDA and MEN 11079 ID(50) values were also significantly different from each other (K-562: P=0.038; MNCs: P=0.003). Moreover, the range was 0.002-4.300 microM for IDA and 0.002-0.670 microM for MEN 11079, in the MNCs. Therefore, the latter appeared to assure a smaller variability of response in the AML cells. Apoptosis assays (performed using **Annexin**-V assay and propidium iodide) and cell cycle studies demonstrated that the MEN 11079 effective concentration was 10-fold lower than the DOXO and IDA ones. **MDR** (Pgp and MRP1 proteins), as measured by semiquantitative RT-PCR, cytofluorimetric and functional analysis of proteins, was similarly elicited by IDA and MEN 11079. In conclusion, the response of the cells to the new anthracycline indicates that there is greater cytotoxic activity of this molecule than IDA and DOXO. Its narrower ID(50) range may allow for a more predictable response in the clinical setting.
ACCESSION NUMBER: 2003468952 MEDLINE
DOCUMENT NUMBER: 22804432 PubMed ID: 12921951
TITLE: In vitro antileukemic effect of a new anthracycline analogue, MEN 11079.
AUTHOR: Biscardi Monica; Caporale Roberto; Pagliai Gabriella; Leoni Franco; Bernabei Pietrantonio; Santini Valeria; Ciolli Stefania; Grossi Alberto
CORPORATE SOURCE: U.O. Hematology, Azienda Ospedaliera Careggi, University of Florence, Viale Morgagni 85, 50134 Florence, Italy.
SOURCE: LEUKEMIA RESEARCH, (2003 Dec) 27 (12) 1125-34.
Journal code: 7706787. ISSN: 0145-2126.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20031009
Last Updated on STN: 20031105
Entered Medline: 20031104

L3 ANSWER 2 OF 59 MEDLINE on STN
TI Functional androgen receptor confers sensitization of androgen-independent prostate cancer cells to anticancer therapy via caspase activation.
AB Therapeutic resistance remains an unresolved problem in the clinical management of human prostate cancer (PC). Despite initial positive response to androgen ablation therapy (AAT), virtually all PC patients will relapse due to acquisition of hormone refractory disease and selective outgrowth of tumor cells with **multidrug resistance** phenotype. We here provide the first experimental evidence that restoring a functional androgen receptor (AR) in the androgen-independent prostate cancer PC3 cells enhances their sensitivity to growth arrest and suppresses their colony-forming ability in response to paclitaxel and gamma-irradiation. Furthermore, functional AR increases the susceptibility of these cells to the apoptotic potentials of therapeutic agents, as evidenced by an increase in caspase activity, **annexin** V binding, and internucleosomal DNA fragmentation, by inducing caspase activation. The abrogation of the cytotoxic effects by 4-hydroxyflutamide suggests a crucial role for AR activation in enhancing the therapeutic sensitivity of these cells in a ligand-independent fashion. Our data thus demonstrate that a functional AR is a prerequisite for effective therapeutic response and that aberrant expression or blockade by AAT may trigger pathways leading to emergence of PC cells with therapeutic resistance phenotype. Since the mainstay of primary therapy for PC has been AAT by pharmaco-therapeutic or surgical means, this study thus provides a new frontier for revising the AAT therapeutic strategy in conjunction with radiation and/or chemotherapeutic agents.
ACCESSION NUMBER: 2003438023 IN-PROCESS
DOCUMENT NUMBER: 22859441 PubMed ID: 13679064
TITLE: Functional androgen receptor confers sensitization of androgen-independent prostate cancer cells to anticancer therapy via caspase activation.
AUTHOR: Davis Rodney; Jia Dingwu; Cinar Bekir; Sikka Suresh C; Moparty Krishnarao; Zhau Haiyen E; Chung Leland W; Agrawal Krishna C; Abdel-Mageed Asim B
CORPORATE SOURCE: Department of Urology, Tulane University Health Sciences Center, New Orleans, LA, USA.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2003 Oct 3) 309 (4) 937-45.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030923
Last Updated on STN: 20031018

L3 ANSWER 3 OF 59 MEDLINE on STN
TI The relationship between drug sensitivity and expression of drug resistance gene mutations in non-small cell lung cancer.
AB OBJECTIVE: To study the relationship between the expression of drug resistance genes and the results of drug sensitivity test. METHODS: Surgical or biopsy specimens from 48 patients with non-small cell lung cancer (NSCLC) were measured for drug sensitivity by **Annexin** V combined with PI using flow cytometry. The drug resistance genes **MDR**(1), GST-pi and MPR were measured by RT-PCR. The relationship between expression of drug resistance gene mutations and the drug sensitivity of lung cancer was analyzed. RESULTS: The anti-tumor

cytotoxicity of MMC, DDP, VDS, NVB, TAX, GEM, VP-16 and VCR were measured, and their respective tumor inhibition rates were (10.3 +/- 17.1)%, (20.7 +/- 22.2)%, (5.6 +/- 14.9)%, (7.9 +/- 16.2)%, (15.7 +/- 21.8)%, (11.2 +/- 13.8)%, (9.7 +/- 20.1)%, and (4.7 +/- 8.7)%. The positive rates of **MDR**(1), MRP and GST-pi expression were 67% (32/48), 42% (20/48), and 48% (23/48) respectively. There was no association between the expression of drug resistance genes MRP and GST-pi and the pathology or the stage of lung cancer. Interestingly, the over-expression of MRP was related to drug resistance to NVB, VDS and MMC; while the over-expression of GST-pi was related to resistance to DDP. No relationship was found between **MDR**(1) over-expression and drug resistance. CONCLUSION: The expression of some drug resistance genes is related to drug sensitivity test. The detection of the genes may be clinically useful in the administration of chemotherapy.

ACCESSION NUMBER: 2003111698 MEDLINE
DOCUMENT NUMBER: 22512168 PubMed ID: 12622891
TITLE: The relationship between drug sensitivity and expression of drug resistance gene mutations in non-small cell lung cancer.
AUTHOR: Han Baohui; Liao Meilin; Su Jianzhong; Feng Jiuxian; Wang Enzhong; Dong Qianggang
CORPORATE SOURCE: Department of Pulmonology, Shanghai Chest Hospital, Shanghai 200030, China.
SOURCE: CHUNG-HUA CHIEH HO HO HU HSI TSA CHIH CHINESE JOURNAL OF TUBERCULOSIS AND RESPIRATORY DISEASES, (2002 Dec) 25 (12) 727-31.
Journal code: 8712226. ISSN: 1001-0939.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030308
Last Updated on STN: 20030819
Entered Medline: 20030818

L3 ANSWER 4 OF 59 MEDLINE on STN
TI Interaction between various resistance modifiers and apoptosis inducer 12H-benzo[alpha]phenothiazine.
AB The effect of some resistance modifiers on apoptosis induction by a benzo[alpha]phenothiazine derivative was studied on the L5178Y mouse lymphoma cells (parent) and its multidrug resistant (**MDR**) subline. For evaluation of apoptosis the cells were stained with FITC-labelled **annexin** V and propidium iodide and the results were analysed by flow cytometry. 12H-benzo[alpha]phenothiazine [M627] induced apoptosis both in the parent cells and in the **MDR** cells. The apoptosis induction by [M627] was not affected significantly by post- or pre-treatment with resistance modifiers, while in the cells treated by (+/-)-verapamil before and after apoptosis induction with [M627], the apoptosis was somewhat higher. The resistance modifier compounds alone also induced apoptosis and it was slightly higher in the parent cells than its MDR1/A gene-transformed subline.

ACCESSION NUMBER: 2003024018 MEDLINE
DOCUMENT NUMBER: 22418380 PubMed ID: 12530005
TITLE: Interaction between various resistance modifiers and apoptosis inducer 12H-benzo[alpha]phenothiazine.
AUTHOR: Mucsi Ilona; Varga Andreas; Kawase Masami; Motohashi Noboru; Molnar Joseph
CORPORATE SOURCE: Department of Medical Microbiology, Faculty of General Medicine, University of Szeged, Hungary.
SOURCE: ANTICANCER RESEARCH, (2002 Sep-Oct) 22 (5) 2833-6.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030118
Last Updated on STN: 20030221
Entered Medline: 20030220

L3 ANSWER 5 OF 59 MEDLINE on STN
TI The HMG-CoA reductase inhibitor lovastatin protects cells from the antineoplastic drugs doxorubicin and etoposide.
AB Ras-homologous GTPases are involved in the regulation of genotoxic stress-induced gene expression and cell death. Since they need C-terminal isoprenylation for correct intracellular localization and function, we investigated whether depletion of cells from isopren precursor moieties using the HMG-CoA reductase inhibitor lovastatin affects cellular sensitivity to DNA damaging drugs. Here we show that lovastatin renders cells highly resistant to the tumor-therapeutic compound doxorubicin. Desensitization by lovastatin was reverted by co-treatment with GGPP indicating that inhibition of protein geranylgeranylation is involved in acquired doxorubicin resistance. Lovastatin does not influence cellular sensitivity to DNA damaging compounds such as cisplatin, methyl methanesulfonate and ionizing radiation. The frequency of apoptotic cell death induced by doxorubicin was not affected by lovastatin as shown by both **annexin** V and DNA fragmentation assay. However, lovastatin releases cells from doxorubicin induced G2 blockage. Furthermore, lovastatin protects cells from doxorubicin-induced DNA strand breakage without affecting drug uptake or the expression of **multidrug resistance** protein (**mdr**-1). Since lovastatin confers cross-resistance to the topoisomerase II specific inhibitor etoposide, we suggest desensitization by the statin to be related to topoisomerase II function. The finding that lovastatin renders cells resistant to doxorubicin and etoposide by reducing their genotoxic and cytotoxic effects might have clinical implications for cancer therapy.
ACCESSION NUMBER: 2002477340 MEDLINE
DOCUMENT NUMBER: 22224508 PubMed ID: 12239596
TITLE: The HMG-CoA reductase inhibitor lovastatin protects cells from the antineoplastic drugs doxorubicin and etoposide.
AUTHOR: Bardeleben Renate V; Dunkern Torsten; Kaina Bernd; Fritz Gerhard
CORPORATE SOURCE: Division of Applied Toxicology, Institute of Toxicology, University of Mainz, D-55131 Mainz, Germany.
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, (2002 Oct) 10 (4) 473-9.
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20020920
Last Updated on STN: 20030312
Entered Medline: 20030311

L3 ANSWER 6 OF 59 MEDLINE on STN
TI Modulation of the **multidrug resistance** of glioma by glutathione levels depletion--interaction with Tc-99M-Sestamibi and Tc-99M-Tetrofosmin.
AB We have investigated the effect of glutathione (GSH) depletion on the chemosensitivity of human malignant glioma cell lines: G111, G5 and G152. All the cell lines showed a multidrug resistant (**MDR**) phenotype associated with MRP1 expression, high intracellular levels of GSH, and depolarized plasma membranes. Tc-99M-Sestamibi (MIBI) and Tc-99M-Tetrofosmin (Tfos) were used for monitoring the **MDR** mechanisms. Modulation of GSH content was performed with

butoxysulfoximide (BSO) pre-treatment alone or in combination with GSH ethyl ester. MIBI and Tfos accumulation in the cells was inversely correlated to the GSH content, a higher accumulation was found after BSO pre-treatment and addition of GSH ethyl ester reversed this process. BSO could therefore play a role as a chemosensitizing drug and thus help to overcome **MDR**. However, higher accumulation of MIBI and Tfos was observed even in the sensitive cells suggesting another effect of BSO on the cell physiological characteristics. No sign of apoptosis has been found indicating a possible direct effect on the plasma membrane fluidity and permeability. MIBI and Tfos don't follow the expected behavior of a **MDR** probe in the glioma cells and given the particular morpho-physiological characteristics of these types of tumors, Tfos could be rather used as a marker of the tumor growth and proliferation.

ACCESSION NUMBER: 2002388439 MEDLINE
DOCUMENT NUMBER: 22132687 PubMed ID: 12136521
TITLE: Modulation of the **multidrug resistance** of glioma by glutathione levels depletion--interaction with Tc-99M-Sestamibi and Tc-99M-Tetrofosmin.
AUTHOR: Perek Nathalie; Koumanov Francoise; Denoyer Delphine; Boudard Delphine; Dubois Francis
CORPORATE SOURCE: Department of Biophysics and Image Treatment, Faculty of Medicine, Jacques Lisfranc, Saint Etienne, France.. nathalie.perek@univ-st-etienne.fr
SOURCE: CANCER BIOTHERAPY & RADIOPHARMACEUTICALS, (2002 Jun) 17 (3) 291-302.
Journal code: 9605408. ISSN: 1084-9785.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20020725
Last Updated on STN: 20030128
Entered Medline: 20030127

L3 ANSWER 7 OF 59 MEDLINE on STN
TI Transport of phosphatidylserine via MDR1 (**multidrug resistance** 1)P-glycoprotein in a human gastric carcinoma cell line.
AB The ATP-binding cassette transporter **multidrug resistance** 1 P-glycoprotein (MDR1 Pgp) has been implicated with the transport of lipids from the inner to the outer leaflet of the plasma membrane. While this has been unambigously shown for the fluorescent lipid analogues [N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]hexanoyl (C6-NBD)-phosphatidylcholine, -phosphatidylethanolamine, -sphingomyelin and -glucosylceramide, by using a novel approach we have now found significantly increased outward transport also for C6-NBD-phosphatidylserine (C6-NBD-PS) in EPG85-257 human gastric carcinoma cells overexpressing MDR1 (coding for MDR1 Pgp). The increased transport of C6-NBD-PS is mediated by MDR1 Pgp, shown by transport reduction nearly to the level of controls in the presence of MDR1 Pgp inhibitors [PSC 833, cyclosporin A and dexniguldipine hydrochloride (Dex)]. Addition of MK 571, a specific inhibitor of the **MDR** protein MRP1, does not decrease transport in either of the two cell lines. The plasma-membrane association of FITC-**annexin** V, a fluorescent protein conjugate binding PS, is significantly increased in MDR1-overexpressing cells as compared with controls, and can be reduced by an MDR1 Pgp inhibitor. This suggests that MDR1 Pgp transports endogenous PS, the lipid exhibiting the most pronounced transverse asymmetry in the plasma membrane.

ACCESSION NUMBER: 2002329193 MEDLINE
DOCUMENT NUMBER: 22067080 PubMed ID: 12071854
TITLE: Transport of phosphatidylserine via MDR1 (**multidrug resistance** 1)P-glycoprotein in a human gastric carcinoma cell line.

AUTHOR: Pohl Antje; Lage Hermann; Muller Peter; Pomorski Thomas; Herrmann Andreas
CORPORATE SOURCE: Institute of Biology/Biophysics, Humboldt University Berlin, Invalidenstrasse 43, 10115 Berlin, Germany.
SOURCE: BIOCHEMICAL JOURNAL, (2002 Jul 1) 365 (Pt 1) 259-68. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020620
Last Updated on STN: 20020727
Entered Medline: 20020726

L3 ANSWER 8 OF 59 MEDLINE on STN
TI Myeloid-lymphoid initiating cells (ML-IC) are highly enriched in the rhodamine-c-kit(+)CD33(-)CD38(-) fraction of umbilical cord CD34(+) cells.
AB OBJECTIVE: The study of hematopoietic stem cells (HSC) is limited by lack of specific markers for HSC. Rhodamine 123 (Rho) is one of the substrates of P-glycoprotein (Pgp), and the presence of active Pgp can be shown by the efflux of Rho. Rho can also be used to measure the mitochondrial transmembrane potential (energy state) of a cell. We reasoned that selection of hematopoietic progenitors using a combination of Rho efflux and phenotypic markers might be superior to use of phenotypic markers alone. MATERIALS AND METHODS: We used the myeloid-lymphoid initiating cell (ML-IC) assay as functional measure of primitive progenitors. Umbilical cord blood CD34(+)CD33(-)CD38(-), CD34(+)CD33(-)CD38(-)Rho(-), and CD34(+)CD33(-)CD38(-)Rho(-)c-kit(+) cells were sorted singly onto AFT024 feeders to assess their capacity to become ML-IC. RESULTS: The frequency of ML-IC in CD34(+)CD33(-)CD38(-)Rho(-) cells was significantly higher (15 +/- 0.4%) than that in CD34(+)CD33(-)CD38(-) cells (6.2 +/- 0.9%, $p < 0.05$). However, the frequency of long-term culture-initiating cells (LTC-IC) (17 +/- 3% vs 12 +/- 1.5%) and natural killer culture-initiating cells (NK-IC) (25 +/- 3% vs 20 +/- 4%) was similar in the two populations. Following the treatment of CD34(+)CD33(-)CD38(-)Rho(-) cells with verapamil, which blocks Pgp function, no increase in ML-IC was detected compared with CD34(+)CD33(-)CD38(-) cells (6 +/- 0.7%), suggesting that differences in the energy state, which is reflected by Rho staining after verapamil treatment, cannot be used as a criterion to identify human HSC. Further selection of CD34(+)CD33(-)CD38(-)Rho(-) cells based on expression of c-kit significantly increased the frequency of ML-IC, LTC-IC and NK-IC by 1.75-, 1.3-, and 1.8-fold, respectively. CONCLUSION: Combining the function of Pgp and phenotypic features of hematopoietic progenitors enriches the frequency of cord blood ML-IC to greater than 25%. Use of such enriched populations will allow us to characterize the biological behavior of human HSC.
ACCESSION NUMBER: 2002318669 MEDLINE
DOCUMENT NUMBER: 22057778 PubMed ID: 12063025
TITLE: Myeloid-lymphoid initiating cells (ML-IC) are highly enriched in the rhodamine-c-kit(+)CD33(-)CD38(-) fraction of umbilical cord CD34(+) cells.
AUTHOR: Liu Hsingjin; Verfaillie Catherine M
CORPORATE SOURCE: Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis 55455, USA.
CONTRACT NUMBER: P01-CA-65493-6 (NCI)
SOURCE: EXPERIMENTAL HEMATOLOGY, (2002 Jun) 30 (6) 582-9. Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207

ENTRY DATE: Entered STN: 20020614
Last Updated on STN: 20021218
Entered Medline: 20020710

L3 ANSWER 9 OF 59 MEDLINE on STN

TI Induction of **multidrug resistance** in MOLT-4 cells by anticancer agents is closely related to increased expression of functional P-glycoprotein and MDR1 mRNA.

AB PURPOSE: The aim of this study was to investigate the **multidrug resistance** (**MDR**) pattern, **MDR** gene and P-glycoprotein (P-gp) expression, and P-gp function in drug-induced human T-lymphoblastoid leukemia MOLT-4 sublines. METHODS: The **MDR** sublines were developed by exposing the parental MOLT-4 cells to stepwise increasing concentrations of anticancer drugs daunorubicin (DNR), vinblastine (VBL) and doxorubicin (DOX). Degrees of resistance were assessed in terms of IC(50) values in an MTT assay and the P-gp function was evaluated in terms of rhodamine 123 (Rh123) accumulation and efflux. The percentage of cells undergoing apoptosis was determined by flow cytometry after staining with **annexin** V-FITC and propidium iodide. The levels of P-gp and **MDR** mRNA expression were estimated using the PE-conjugated anti-P-gp monoclonal antibody 17F9 and quantitative real-time reverse transcription-polymerase chain reaction. RESULTS: Three MOLT-4 sublines were established and revealed a 2- to 115-fold resistance to the anticancer reagents DNR, VBL and DOX as compared to the parental cell line. The highest **MDR** was expressed in MOLT-4/DNR cells, which was overcome by the P-gp modulator, cyclosporin A (CsA). The resistant sublines showed a decreased accumulation and an increased efflux of Rh123 in proportion to the degree of resistance, and these were completely reversed in the presence of 8 microM CsA. The decreased apoptotic response in these cell lines was clearly associated with the degree of drug resistance. P-gp antigen and MDR1 mRNA were highly expressed in both the MOLT-4/DNR and MOLT-4/DOX sublines. Less-resistant MOLT-4/VBL cells expressed lower levels of MDR1 mRNA and P-gp, even though the cell line was established by exposing the parental MOLT-4 cells to VBL for longer (5 months) than to the other two reagents (3 months). CONCLUSIONS: MOLT-4 cells were able to acquire a high level of drug resistance by culturing the cells in the presence of certain anticancer drugs, and acquisition of the resistance was relatively reagent-specific. The degrees of resistance to the anticancer drugs were well correlated with the expressions of MDR1 mRNA and functional P-gp, and were also associated with a decreased response to apoptosis.

ACCESSION NUMBER: 2002318051 MEDLINE
DOCUMENT NUMBER: 21972412 PubMed ID: 11976833
TITLE: Induction of **multidrug resistance** in MOLT-4 cells by anticancer agents is closely related to increased expression of functional P-glycoprotein and MDR1 mRNA.
AUTHOR: Liu Zhen-Li; Onda Kenji; Tanaka Sachiko; Toma Tsugutoshi; Hirano Toshihiko; Oka Kitaro
CORPORATE SOURCE: Department of Clinical Pharmacology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, Hachioji, Japan.
SOURCE: CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2002 May) 49 (5) 391-7.
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020614
Last Updated on STN: 20030105
Entered Medline: 20020627

L3 ANSWER 10 OF 59 MEDLINE on STN

TI Novel triterpenoid CDDO-Me is a potent inducer of apoptosis and differentiation in acute myelogenous leukemia.

AB It has been shown that the novel synthetic triterpenoid CDDO inhibits proliferation and induces differentiation and apoptosis in myeloid leukemia cells. In the current study the effects of the C-28 methyl ester of CDDO, CDDO-Me, were analyzed on cell growth and apoptosis of leukemic cell lines and primary acute myelogenous leukemia (AML). CDDO-Me decreased the viability of leukemic cell lines, including multidrug resistant (**MDR**)-1-overexpressing, p53(null) HL-60-Dox and of primary AML cells, and it was 3- to 5-fold more active than CDDO. CDDO-Me induced a loss of mitochondrial membrane potential, induction of caspase-3 cleavage, increase in **annexin** V binding and DNA fragmentation, suggesting the induction of apoptosis. CDDO-Me induced pro-apoptotic Bax protein that preceded caspase activation. Furthermore, CDDO-Me inhibited the activation of ERK1/2, as determined by the inhibition of mitochondrial ERK1/2 phosphorylation, and it blocked Bcl-2 phosphorylation, rendering Bcl-2 less anti-apoptotic. CDDO-Me induced granulo-monocytic differentiation in HL-60 cells and monocytic differentiation in primary cells. Of significance, colony formation of AML progenitors was significantly inhibited in a dose-dependent fashion, whereas normal CD34(+) progenitor cells were less affected. Combinations with ATRA or the RXR-specific ligand LG100268 enhanced the effects of CDDO-Me on cell viability and terminal differentiation of myeloid leukemic cell lines. In conclusion, CDDO-Me is an **MDR**-1- and a p53-independent compound that exerts strong antiproliferative, apoptotic, and differentiating effects in myeloid leukemic cell lines and in primary AML samples when given in submicromolar concentrations. Differential effects of CDDO-Me on leukemic and normal progenitor cells suggest that CDDO-Me has potential as a novel compound in the treatment of hematologic malignancies.

ACCESSION NUMBER: 2002055056 MEDLINE
DOCUMENT NUMBER: 21628800 PubMed ID: 11756188
TITLE: Novel triterpenoid CDDO-Me is a potent inducer of apoptosis and differentiation in acute myelogenous leukemia.
AUTHOR: Konopleva Marina; Tsao Twee; Ruvolo Peter; Stiouf Irina; Estrov Zeev; Leysath Clinton E; Zhao Shourong; Harris David; Chang Shirong; Jackson C Ellen; Munsell Mark; Suh Nanjoo; Gribble Gordon; Honda Tadashi; May W Stratford; Sporn Michael B; Andreeff Michael
CORPORATE SOURCE: Department of Blood and Marrow Transplantation, Section of Molecular Hematology and Therapy, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.
CONTRACT NUMBER: CA16672 (NCI)
CA44649 (NCI)
CA49639 (NCI)
CA55164 (NCI)
R01 CA 78814 (NCI)
SOURCE: BLOOD, (2002 Jan 1) 99 (1) 326-35.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20021214
Entered Medline: 20020128

L3 ANSWER 11 OF 59 MEDLINE on STN

TI Effects of butaclamol, clopenthixol, mepromazine and cannabinol stereoisomers on apoptosis induction.

AB The efflux pump of multidrug resistant **mdr** cells have different sensitivities to some stereoisomeric forms of CNS-active compounds. The ABC transporters of **mdr** cells were more sensitive to

(-)butaclamol than to its stereoisomeric counterpart (8), which may function to alter the membrane structure. We suppose that the drug-accessible membrane structure possesses an important role in the induction (or prevention) of apoptosis. Therefore the apoptosis-inducing effect of three stereoisomeric pairs was studied on mouse lymphoma cells. In these experiments levo- and dextromepromazine had similiar effects. The cis- and trans-clopenthixol were less effective in apoptosis induction than the 12H-benzo(a)-phenothiazine used as a positive control. The effect of stereoisomeric pairs on induced apoptosis was studied when the cells were exposed to the stereoisomers for 60 minutes before subjection apoptosis induction by benzo(a)phenothiazine, a well-known apoptosis inducer. Then the pretreated cells were exposed to 12H-benzo(a)-phenothiazine for 60 minutes. The samples were washed and incubated for 24 hours. The cells were stained with **annexin**-V-FITC and propidium iodine and investigated by flow cytometry. The **mdr** cells with increased membrane integrity may result in the preferential killing of multidrug resistant cancer cells in the presence of some stereoisomers.

ACCESSION NUMBER: 2001678077 MEDLINE
DOCUMENT NUMBER: 21580870 PubMed ID: 11724344
TITLE: Effects of butaclamol, clopenthixol, mepromazine and cannabinol stereoisomers on apoptosis induction.
AUTHOR: Varga A; Sabat R; Mucsi I; Flores V C; Kaiser H E; Molnar J
CORPORATE SOURCE: Department of Molecular Parasitology, Humboldt University, Berlin, Germany.
SOURCE: ANTICANCER RESEARCH, (2001 Jul-Aug) 21 (4A) 2709-12. Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011129
Last Updated on STN: 20020123
Entered Medline: 20011207

L3 ANSWER 12 OF 59 MEDLINE on STN
TI Non-steroidal anti-inflammatory agent ibuprofen-induced apoptosis, cell necrosis and cell cycle alterations in human leukemic cells in vitro.
AB The cytotoxic activity of the non-steroidal anti-inflammatory agent ibuprofen to human promyelocytic leukemia cell line HL-60, its multidrug-resistant subline HL-60/VCR (**MDR**-1 gene coded P-glycoprotein), as well as myeloma U266 and B-lymphoblastoid ARH-77 cell lines was demonstrated with the aid of flow cytometric analysis. Ibuprofen inhibited proliferation and induced apoptosis (detected as sub-G0 nuclei, fluorescein diacetate staining, **Annexin**-V binding cells and agarose electrophoretic detection of nucleosomal DNA fragmentation) in promyelocytic cells and, to a lesser extent, in U266 and ARH-77 cells.

ACCESSION NUMBER: 2001535506 MEDLINE
DOCUMENT NUMBER: 21466982 PubMed ID: 11583291
TITLE: Non-steroidal anti-inflammatory agent ibuprofen-induced apoptosis, cell necrosis and cell cycle alterations in human leukemic cells in vitro.
AUTHOR: Jakubikova J; Duraj T; Takacsova X; Hunakova L; Chorvath B; Sedlak J
CORPORATE SOURCE: Cancer Research Institute, Slovak Academy of Sciences, Bratislava, Slovak Republic.. exonjana@savba.sk
SOURCE: NEOPLASMA, (2001) 48 (3) 208-13. Journal code: 0377266. ISSN: 0028-2685.
PUB. COUNTRY: Slovakia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011004
Last Updated on STN: 20011022
Entered Medline: 20011018

L3 ANSWER 13 OF 59 MEDLINE on STN
TI **Multidrug-resistance** phenotype and clinical responses to gemtuzumab ozogamicin.
AB Expression of **multidrug resistance** (**MDR**) features by acute myeloid leukemia (AML) cells predicts a poor response to many treatments. The **MDR** phenotype often correlates with expression of P-glycoprotein (Pgp), and Pgp antagonists such as cyclosporine (CSA) have been used as chemosensitizing agents in AML. Gemtuzumab ozogamicin, an immunoconjugate of an anti-CD33 antibody linked to calicheamicin, is effective monotherapy for CD33(+) relapsed AML. However, the contribution of Pgp to gemtuzumab ozogamicin resistance is poorly defined. In this study, blast cell samples from relapsed AML patients eligible for gemtuzumab ozogamicin clinical trials were assayed for Pgp surface expression and Pgp function using a dye efflux assay. In most cases, surface expression of Pgp correlated with Pgp function, as indicated by elevated dye efflux that was inhibited by CSA. Among samples from patients who either failed to clear marrow blasts or failed to achieve remission, 72% or 52%, respectively, exhibited CSA-sensitive dye efflux compared with 29% (P =.003) or 24% (P <.001) among samples from responders. In vitro gemtuzumab ozogamicin--induced apoptosis was also evaluated using an **annexin** V--based assay. Low levels of drug-induced apoptosis were associated with CSA-sensitive dye efflux, whereas higher levels correlated strongly with achievement of remission and marrow blast clearance. In vitro drug-induced apoptosis could be increased by CSA in 14 (29%) of 49 samples exhibiting low apoptosis in the absence of CSA. Together, these findings indicate that Pgp plays a role in clinical resistance to gemtuzumab ozogamicin and suggest that treatment trials combining gemtuzumab ozogamicin with **MDR** reversal agents are warranted. (Blood. 2001;98:988-994)
ACCESSION NUMBER: 2001446293 MEDLINE
DOCUMENT NUMBER: 21384755 PubMed ID: 11493443
TITLE: **Multidrug-resistance** phenotype and clinical responses to gemtuzumab ozogamicin.
AUTHOR: Linenberger M L; Hong T; Flowers D; Sievers E L; Gooley T A; Bennett J M; Berger M S; Leopold L H; Appelbaum F R; Bernstein I D
CORPORATE SOURCE: Clinical Research Division, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA.. linen@u.washington.edu
SOURCE: BLOOD, (2001 Aug 15) 98 (4) 988-94.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20020716
Entered Medline: 20010920

L3 ANSWER 14 OF 59 MEDLINE on STN
TI Potent induction of apoptosis by beta-lapachone in human multiple myeloma cell lines and patient cells.
AB BACKGROUND: Human multiple myeloma (MM) remains an incurable hematological malignancy. We have reported that beta-lapachone, a pure compound derived from a plant, can induce cell death in a variety of human carcinoma cells, including ovary, colon, lung, prostate, pancreas, and breast, suggesting a wide spectrum of anticancer activity. MATERIALS AND METHODS: We first studied antisurvival effects of beta-lapachone in human MM cells by colony

formation assay. To determine whether the differential inhibition of colony formation occurs through antiproliferative activity, we performed MTT assays. The cytotoxicity of beta-lapachone on human peripheral blood mononuclear cells was also measured by MTT assay. To determine whether the cell death induced by beta-lapachone occurs through necrosis or apoptosis, we used the propidium iodide staining procedure to determine the sub-GI fraction, **Annexin**-V staining for externalization of phosphatidylserine, and fragmentation of cellular genomic DNA subjected to gel electrophoresis. To investigate the mechanism of anti-MM activity, we examined Bcl-2 expression, cytochrome C release, and poly (ADP ribose) polymerase cleavage by Western blot assay. RESULTS: We found that beta-lapachone (less than 4 microM) inhibits cell survival and proliferation by triggering cell death with characteristics of apoptosis in ARH-77, HS Sultan, and MM.1S cell lines, in freshly derived patient MM cells (MM.As), MM cell lines resistant to dexamethasone (MM.1R), doxorubicin (DOX.40), mitoxantrone (MR.20), and mephalan (LR5). Importantly, after treatment with beta-lapachone, we observed no apoptosis in peripheral blood mononuclear cells in either quiescent or proliferative states, freshly isolated from healthy donors. In beta-lapachone treated ARH-77, cytochrome C was released from mitochondria to cytosol, and poly (ADP ribose) polymerase was cleaved, signature events of apoptosis. Finally, the apoptosis induced by beta-lapachone in MM cells was not blocked by either interleukin-6 or Bcl-2, which confer **multidrug resistance** in MM. CONCLUSIONS: Our results suggest potential therapeutic application of beta-lapachone against MM, particularly to overcome drug resistance in relapsed patients.

ACCESSION NUMBER: 2001441865 MEDLINE
DOCUMENT NUMBER: 21366316 PubMed ID: 11474117
TITLE: Potent induction of apoptosis by beta-lapachone in human multiple myeloma cell lines and patient cells.
AUTHOR: Li Y; Li C J; Yu D; Pardee A B
CORPORATE SOURCE: Dana-Farbe Cancer Institute, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, USA.. Youzhi_Li@dfci.harvard.edu
CONTRACT NUMBER: RO1 CA61253 (NCI)
SOURCE: MOLECULAR MEDICINE, (2000 Dec) 6 (12) 1008-15. Journal code: 9501023. ISSN: 1076-1551.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010820
Entered Medline: 20010816

L3 ANSWER 15 OF 59 MEDLINE on STN
TI Time- and concentration-dependent apoptosis and necrosis induced by free and HPMA copolymer-bound doxorubicin in human ovarian carcinoma cells.
AB A2780 sensitive and A2780/AD doxorubicin (DOX) resistant human ovarian carcinoma cells were exposed to different concentrations (0.25, 0.5, 1, 5 and 10xIC(50)) of free and HPMA copolymer-bound DOX for 12, 24, 36, 48, 60 and 72 h. Apoptosis and necrosis were evaluated using the FITC-conjugated **annexin** V and propidium iodide staining. The data obtained showed that the induction of apoptosis and necrosis by both free DOX and HPMA copolymer-bound DOX were time- and concentration-dependent. The data also showed significant differences between the drugs. It was found that: (i) under the action of HPMA copolymer-bound doxorubicin the alterations in the plasma membrane permeability preceded disturbances in cellular metabolism; (ii) HPMA copolymer-bound doxorubicin kills the cells mainly by necrosis; (iii) HPMA copolymer-bound doxorubicin is a more effective anticancer drug than free doxorubicin.

ACCESSION NUMBER: 2001052226 MEDLINE

DOCUMENT NUMBER: 20473531 PubMed ID: 11018556
TITLE: Time- and concentration-dependent apoptosis and necrosis induced by free and HPMA copolymer-bound doxorubicin in human ovarian carcinoma cells.
AUTHOR: Demoy M; Minko T; Kopeckova P; Kopecek J
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA.
CONTRACT NUMBER: CA 51578 (NCI)
SOURCE: JOURNAL OF CONTROLLED RELEASE, (2000 Oct 3) 69 (1) 185-96. Journal code: 8607908. ISSN: 0168-3659.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001213